REMARKS

Reconsideration is respectfully requested. Claims 1-23, 28, and 37 have been cancelled. Claims 24-27, 29-36 and 38-42 are pending and stand rejected.

Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Rejections under 35 USC § 103(a)

The Examiner has rejected claims 24-27, 29-31, 33, 34, 41, and 42 over U.S. Patent No. 5,320,808 to Holen *et al.* ("Holen") in view of U.S. Patent No. 5,532,128 to Eggers ("Eggers"). In addition, the Examiner rejects claim 32 over Holen and Eggers in further view of U.S. Patent No. 4,599,303 to Yabusaki ("Yabusaki"); claims 35, 36, 38, and 39 over Holen and Eggers in further view of U.S. Patent No. 5,780,234 to Meade ("Meade"); and claim 40 over Holen, Eggers, and Meade in further view of U.S. Patent No. 6,288,221 to Grinstaff ("Grinstaff"). Fundamentally, the obviousness rejections all rely on the combination of Holen and Eggers. The Examiner has failed to provide the requisite *prima facie* case for obviousness.

As is shown below, the Holen system requires that air be present in the sample to be measured. Eggers relies on electronic detection using changes in permittivity, or the dielectric between the two electrodes, upon binding of the target nucleic acid. If air is introduced into the Eggers system, the dielectric of air (approximately 1) would completely mask the smaller changes in an aqueous solution (dielectric of approximately 80), thus rendering the combination unsuitable for its intended use.

Further, Holen requires carousel which is configured to receive a number of reaction cartridges. Once inserted, a cartridge is rotated to various predetermined positions, such as for example an optical reading position or a wash position. Eggers system requires uninterrupted electrical connection between its array of test sites and its detection and recognition circuitry. If a rotatable carousel was introduced into the Eggers' system, this electrical connection would be interrupted and thus hinder the detection of any probe binding to the target sites its circuitry.

As such, the combination of the references do not render the claims obvious.

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A. Explanation of Holen Technology

1. Air must be present in the sample.

Holen discloses that a carousel is arranged "to provide agitation required for processing samples and reagents." (Col. 6 lines 29-31). Specifically, Holen describes the carousel containing samples "disposed on a tilted axis" (Col. 6 lines 45-46) and a reaction cartridge 80 suitable for insertion into the carousel (see Col. 6 lines 26-32 and Figures 2 and 5), wherein each cartridge contains a "plurality of isolated test sites 84 each composed of binding layer material encircled by a moat 99 of air space" (Col. 14 lines 22-25 and Figure 8). Thus, fluid agitation on a tilted axis as described by Holen requires the presence of air in a sample. Like all non-conducting materials, air does not allow electrical conductivity such as that necessary in the electrochemical detection method of Eggers.

2. Electrically conductive contacts are not attached directly to the detection wells.

Holen discloses methods of optically detecting a target analyte. In its summary of the invention, Holen discloses that the "reaction well is configured to provide direct optical access to the test sites." (Holen, Col. 4, lines 59-60). Reaction cartridges containing test wells are rotated to produce "desirable agitation of the fluids in a reaction wells" so as to allow different biochips to be analyzed (Holen, Col. 6 lines 45-50). The rotational system of Holen detects compounds in the system by using an optical reader that:

> emits a beam of optical radiation onto a small portion of the test site ... [T]he optical detector converts the intensity of the optical radiation reflected by the diffuse surface of the test site into the electrical signal. The signal is then processed to obtain the optical density value of the test site 84 which is directly related to the concentration of the binding component of interest in the biological sample.
> [Holen, Column 8, lines 21-29]

Thus, Holen's "carousel 18 serves two primary function; first as a "means for holding and conveying reaction cartridges 80 in order to position the cartridges to receive sample" and second "as a very precise optical bench, accurately positioning each reaction cartridge 80 relative to an optical reader 32." (Col. 6 lines 24-35) In each case, the reaction cartridges change position once inserted into the carousel.

6

B. Explanation of Eggers Technology

1. Electrochemical detection occurs in an aqueous solution.

Eggers discloses that its measurements are made in "a low concentration aqueous solution." (Col. 6 lines 52-54). This method of detecting the presence of target DNA is based on measuring a frequency dependent effect or dielectric dispersion (Col. 5 lines 54 through Column 7 line 58. Specifically, Eggers discloses that dielectric characterization is "primarily made by measuring the dielectric constant, or equivalently, relative permittivity ϵ." (Col. 5 lines 61-65). In addition, Eggers describes

> Utilizing a four-terminal parallel plate test fixture, the electrical properties of DNA in a low concentration aqueous solution can be obtained. Four-terminal fixtures are typically used in dielectric measurements to minimize unwanted residual factors arising from self and/or mutual induction between the leads. Graphs of DNA dielectric dispersion represented by ϵ' and ϵ'' are well known and are described in greater detail in Takashima, S., J. Mol. Biol. 7:455-467 (1963), which is incorporated by reference herein. The dispersion arises from the negatively charged phosphate groups assembled in the backbone of the DNA molecule which attract the counter-ions in the solution. Although the DNA has no helix dipole moment (since it is a simple linear polyphosphate), a large dipole is induced from the counter ions in the solution being reoriented along the DNA backbone under the influence of an applied electric field. The dispersion, and hence relaxation frequency, is dependent upon the ion mobility, permittivity of the surrounding ionic medium, and the length of the DNA according to
>
> $$f_r = (2\mu z q)^2/\pi\epsilon)/L^2 \qquad [(1)]$$
>
> where:
> L is the effective molecular length of the DNA
> q is the electron charge
> μ is the counter-ion surface mobility,
> z is the number of ions in the surrounding ionic solution,
> and
> ϵ is the effective permittivity of the surrounding ionic solution of z ions.
> [See Col. 6 line 52 through Col. 7 line 14]

2. Electrochemical detection is based on changes in dielectric constants.

It is well established that air and water have different dielectric constants. The dielectric constant of air is approximately 1 (See Electronic Engineer's Reference Book," Fifth Edition, Ed. F. F. Mazda, Butterworths, London, UK, 1983; a copy of the relevant pages are included) and the dielectric constant of water is approximately 80. Eggers employs an aqueous solution to provide a dielectric constant suitable for measuring the binding of probe to target.

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It is well known in the art that a configuration of two conductive electrodes separated by an insulating layer constitutes a capacitor. Eggers uses a two-electrode sensor in the form of a capacitor as a detector with an aqueous solution as the dielectric between the two electrodes. The reference discloses that the "material under test acts as the dielectric located between the two plates." (Col. 4 lines 59-60) Samples are loaded onto test sites 14 to test for any binding of target 28 to probe 26 as shown in Figures 1-3.

Permittivity is identical to the dielectric constant of the test sample. When the insulator between the two plates (electrodes) is vacuum, the capacitance, C, (which is the amount of charge per volt that may be stored on the plates) of the capacitor is

$$C = \epsilon_0 A/d \qquad (2)$$

where ϵ_0 is the dielectric constant (or permittivity) of free space (i.e. vacuum), A is the surface area of the electrodes and d is the distance between the electrodes. When the insulator between the two plates (electrodes) of a capacitor is any material other than a vacuum, the capacitance is

$$C = \epsilon \epsilon_0 A/d \qquad (3)$$

where ϵ is the dielectric constant (or permittivity) of the insulating material. Thus, the amount of charge per volt that may be stored is a function of the size of the plates, their distances, and how "polarizable" the medium between them is, which can effect how easy it is to build up a charge between the plates.

3. Electrical contacts are required at all times.

Eggers discloses measuring changes in electrical properties that require electrical contacts such as frequency ranges, conductance, and permittivity. (e.g. Eggers, Col. 5, lines 54-62). Specifically, Eggers provides that "[c]hanges in the dielectric properties formed by the test sites 14 of FIGS. 2a-b are detected by detection circuitry 16." (Eggers, col. 4, lines 61-63).

C.   Combining Holen and Eggers Renders a Combination Unsuitable for its Intended Use

1. The combined references do not render the claims obvious.

The Examiner bears the burden of establishing that the cited references provide the requisite motivation or suggestion to combine their teachings. There must be some valid scientific principle or legal precedent supporting the combination of the methods taught by the reference. See M.P.E.P. § 2144. In the present case, the scientific principles of operation of

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each of the references are incompatible with each other because combination of the teachings of Holen and Eggers would not result in a functional device. Thus, there is no motivation or suggestion to combine the references.

In addition, if "the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)" M.P.E.P. § 2143.01 VI. In the present case, the combination of Holen and Eggers would change the principle of operation of Eggers. Thus, the combined teachings of the references are not sufficient to render the claims *prima facie* obvious.

2. The presence of air in Eggers' system would prevent electrochemical detection.

As discussed above, Eggers employs an aqueous solution to provide a suitable dielectric constant ϵ for measuring the binding of probe to target. Capacitance in Eggers' system must remain constant in order for the accurate measurement of electrical properties. Based on Equation 3, in order to maintain a constant value for C the dielectric constant must also remain constant. The introduction of air as required by Holen in the aqueous solution environment of Eggers varies the dielectric constant. Thus, C will vary and adversely affect the accuracy of any electrical property measurements.

In addition, according to Equation 1 above, as the dielectric constant (permittivity) ϵ increases, the relaxation frequency f_r decreases. Eggers' detection method relies on the f_r measurement as an indicator of whether or not target-probe bonding occurs. (Column 7 lines 45-50) As shown in Figure 5 of the reference, the dielectric dispersion of a test site in which target is bound is detectable at a lower frequency than a test site without bound target. Eggers' method of detection relies on an aqueous solution environment with a dielectric constant of approximately 80. The introduction of air as required by Holen in the Eggers' system would vary the dielectric constant, thereby preventing accurate measurement of target-probe binding via frequency f_r. As such, Holen could not be adapted to use the electrochemical detection methods of Eggers.

3. The use of a rotational system in Eggers would prevent electrochemical detection.

As discussed above, a signal in Holen is detected remotely from the detection wells. Processing the optical signal in the Holen system is accomplished without attaching electrically conductive contacts attached directly to the detection wells. Eggers, by contrast, teaches

9

detecting the presence of analytes by measuring changes in chemoelectrical properties in a sample. Detecting changes in electrical properties in separate wells requires attachment of electrical contacts directly to each separate well. Also, Eggers does not teach inserting first and second biochips into a device as claimed.

The electrochemical properties detected according to Eggers cannot be detected in the rotationally based optical system taught by Holen. In Eggers, electrochemical detection of the samples require that electrical contacts must be maintained with each sample of each biochip. Maintaining separate electrical contacts to measure separate signals in each well of Eggers' system would not be possible in a rotational system of Holen because the samples freely rotate away from the Holen detector. The system would thus not maintain electrical contact with each of the wells. The electrochemical properties detected in Eggers thus could not be detected in the rotational system of Holen.

4. Holen and Eggers cannot be combined to reject the claims under 35 U.S.C. § 103(a).

The introduction of air as required by Holen into the Eggers' system would not result in a functional device. Also, the use of a rotational system as required by Holen in Eggers would not result in a functional device. The motivation to combine the references is not based on a valid scientific principle. Therefore, under M.P.E.P. § 2144, there is no requisite motivation or suggestion to combine their teachings.

The introduction of air or a rotational configuration into Eggers' system would prevent accurate electrochemical detection of target-probe binding. As such, the combination of the references would therefore change Eggers' principle of operation. Therefore under M.P.E.P. § 2143.01 VI., the combined teachings of the references are insufficient to render the claims obvious.

D.   Other Rejections

In addition, none of the additional references (Yabusaka, Meade, and Grinstaff) provide a scientific basis to combine electrochemical methods in first and second biochips, as claimed. None of these references either teach multiple biochips or provide guidance on how to overcome the technical limitations of Holen that render electrochemical detection impossible. Because the scientific principles of operation of each reference are incompatible, there is no motivation or suggestion to combine the references. In addition, a combination of the references would change

10

Eggers' principle of operation. Thus, a combination of Holen and Eggers with one of Yabusaka, Meade, or Grinstaff is insufficient to render the claims obvious.

E.   Rebuttal to Examiner's Arguments

The Examiner argues that one or ordinary skill in the art would have been motivated to combine the references, stating that:

> Eggers teaches the advantages of the disclosed electronic detection apparatus and methodology in relation to optical detection methods utilizing fluorescent labels and including intercalating dyes for DNA analysis. (see col. 2, lines 1 – col. 3, lines 26]

However, as pointed out above, the electrochemical design disclosed by Eggers could not be adapted to the device of Holen. While Eggers show the advantages of electrochemical detection in a single detection well, it fails to show how this could be accomplished using a rotational system of Holen that not only fails to require maintaining electrical contact between the samples and the detection system, but also tilts and agitates samples (which requires air in the system) in a manner wholly incompatible with the methods taught by Eggers. The Examiner also states that

> [t]he strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination.

As discussed above, there is no scientific basis for combining the references because the methods of Holen and Eggers are incompatible. Further, there is also no legal precedent supporting the combination of the particular references. The Examiner has failed to provide the requisite motivation to combine the incompatible references to make the claimed invention.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness and request that the various rejections under 35 U.S.C. §103(a) be withdrawn.

11

CONCLUSION

The present application is therefore in condition for allowance. Early and favorable notification thereof is respectfully requested. If the Examiner believes there are further unresolved issues, the Examiner is invited to call the undersigned at (415) 781-1989.

Respectfully submitted,

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13.1 Characteristics of dielectric materials

13.1.1 General characteristics

Dielectric materials used for radio and electronic capacitors can be grouped into the following five main classes:

(1) Mica, glass, low-loss ceramic, etc.: used for capacitors from a few pF to a few hundred pF.
(2) High-permittivity ceramic: used for capacitors from a few hundred pF to a few tens of thousands of pF.
(3) Paper and metallised paper: used for capacitors from a few thousand pF up to some μF.
(4) Electrolytic (oxide film): used for capacitors from a few μF to many μF.
(5) Dielectrics such as polystyrene, polythene, polythylene terephthalate, polycarbonate, etc.: range of use from a few hundred pF to many μF.

Many factors affect the dielectric properties of a material when it is used in a capacitor; among them being the permittivity, power factor, leakage current, dielectric absorption, dielectric strength, operating temperature, etc.

13.1.2 Summary of properties of capacitor dielectrics

A table of the main characteristics of some dielectric materials used in capacitors is given in *Table 13.1*.

13.1.3 Permittivity (dielectric constant)

The permittivity, dielectric constant or specific inductive capacity of any material used as a dielectric is equal to the ratio of the capacitance of a capacitor using the material as a dielectric, to the capacitance of the same capacitor using vacuum as a dielectric. The permittivity of dry air is approximately equal to one. A capacitor with solid or liquid dielectric of higher permittivity (ε) than air or vacuum can therefore store ε times as much energy for equal voltage applied across the capacitor plates. A few typical figures for capacitor dielectrics are:

	Permittivity (ε)
Vacuum	1.0
Dry air	1.000 59
Polythene, polystyrene, etc.	2.0 to 3.0
Impregnated paper	4.0 to 6.0
Glass and mica	4.0 to 7.0
Ceramic (magnesium titanate, etc.)	Up to 20
Ceramic (titania)	80 to 100
Ceramic (high-ε)* (or high-K)	1000 upwards

Dielectrics can be classified in two main groups—polar and non-polar materials. Polar materials have a permanent unbalance in the electric charges within the molecular structure. The dipoles within the structure consist of molecules whose ends are oppositely charged. These dipoles therefore tend to align themselves in the presence of an alternating electric field (if the frequency is not too high). The resultant oscillation causes a large loss at certain frequencies and at certain temperatures.

13.1.4 Losses in dielectrics

Losses occur due to current leakage, dielectric absorption, etc., depending on the frequency of operation. For a good non-polar

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* The high permittivity in high-ε ceramic capacitors comes from the fact that the electric charges in the molecular structure of the material are very loosely bound and can move almost freely under the polarising voltage, resulting in high total capacitance.

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dielectric the curve relating loss with frequency takes the approximate shape given in *Figure 13.1(a)*. For a polar material the loss-frequency curve may be shown approximately as in *Figure 13.1(b)*.

The variation of permittivity with frequency is negligible so long as the loss is low. Increased losses occur when the process of alignment cannot be completed, owing to molecular collisions, and in these regions there is a fall in permittivity. Viscous drag in the molecular structure limits the frequency at which full alignment can be carried out. If the applied frequency is comparable with the limiting frequency losses still become high.

Equivalent circuits showing series and parallel loss resistance can be given, but are greatly dependent on the system of measurement at any particular frequency. The important criterion is the ratio:

$$\frac{\text{power wasted per cycle}}{\text{power stored per cycle}}$$

This is the power factor of the material and for good dielectrics it is independent of frequency.

13.1.5 Absorption

If a capacitor were completely free from dielectric absorption the initial charging or polarisation current when connected to a d.c. supply would be

$$I = (V/R)e^{-t/CR}$$

where

I = current flowing after a time t
V = applied voltage
R = capacitor series resistance
C = capacitance
e = base of Napierian logs (2.718)

and the polarisation current would die off asymptotically to zero. If R is small, this takes place in a very short time and the capacitor is completely charged. In all solid-dielectric capacitors it is found that, after a fully-charged capacitor is momentarily discharged and left open-circuited for some time, a new charge accumulates
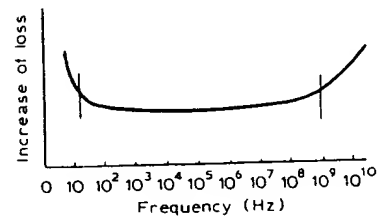
(a)
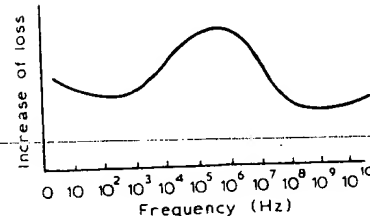
(b)

Figure 13.1 Loss/frequency curve for (a) non-polar dielectric (b) polar dielectric